PATENT
Our Docket: P-IMM 1003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Robbins and Tritz	Group Art Unit: 1635
	Examiner: K. Lacourciere
Serial No: 09/696,791	
Filed: October 25, 2000	
Title: RIBOZYME THERAPY FOR THE TREATMENT OF PROLIFERATIVE SKIN AND EYE DISEASES	

Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

1. I am the first named inventor of the above-identified application.

2. I understand that claims 71 to 78 and 85 to 108 are rejected under 35 U.S.C. § 112, first paragraph, in part, because it is alleged that the subject specification enables only proliferative vitreoretinopathy (PVR), and not generally any proliferative eye disease.

3. In response and in support of the contention that the subject ribozymes are generally effective against proliferative eye disease, attached hereto is Exhibit A. This data show that a ribozyme of the invention is effective in treating another proliferative eye disease, specifically, the post-operative closure of a surgical drainage site

Considered 06-28-03

(called a trabeculectomy) made in the eye that is typically done to relieve intra-ocular pressure due to glaucoma.

4. More specifically, a ribozyme of the invention, SEQ ID NO: 4385, which was formulated in hyaluronic acid for sustained release, was introduced in rabbits to see whether it would be efficacious in reducing post-trabeculectomy hyper-proliferation. The experimental data show that the ribozyme maintained the drainage site clinically open for at least 14 days in most of the rabbits. At termination, 30 days from the procedure, histologic examination of the trabeculectomy site indicated thinning of the sclera and partially opened drainage site in a large number of the rabbits treated with the ribozyme. Thus, the data show that a ribozyme of the invention was effective in treating trabeculectomy.

5. Moreover, the subject specification already provides data showing that a ribozyme of the invention was effective with yet another proliferative disorder, specifically, to prevent scarring in pigs due to surgical incision. See Example 9 of the specification, pages 45-47.

6. Thus, the data attached hereto and disclosed in the subject specification show that a ribozyme of the invention is effective in treating or preventing: a) PVR; b) trabeculectomy; and c) scar formation. The only factor that links these three conditions is that they are proliferative diseases involving a cyclin PCNA. Thus, the data show that a ribozyme of the invention will be effective

in treating any proliferative disease involving a cyclin PCNA, and certainly any such proliferative eye disease.

7. I also understand that claims 71 to 78 and 85 to 108 are rejected under 35 U.S.C. § 112, first paragraph, in part, because it is alleged that the subject specification does not provide guidance with respect to delivery of a ribozyme by any means besides intravitreal injection. In particular, it is alleged that the specification does not provide guidance with respect to delivery by means of a vector.

8. In response, attached hereto as Exhibit B is a chart showing the results of an experiment designed to test the efficacy of delivery by means of a vector of a ribozyme of the invention, SEQ ID NO: 4385. Specifically, human vascular smooth muscle cells were transduced with an adeno-associated virus (AAV) vector adapted to express the PCNA ribozyme. A similar AAV vector expressing an HIV ribozyme was used as a control. As can be seen from Exhibit B, the vector expressing the PCNA was very effective in inhibiting cellular proliferation as indicated by the reduction in the amount of newly synthesized DNA, as measured by a decrease in ^{3}H-thymidine incorporation, which is a standard measure of DNA synthesis.

9. I also understand that claims 71 to 78 and 85 to 108 are rejected under 35 U.S.C. § 112, first paragraph, in part, because it is alleged that use of ribozymes is highly unpredictable. In support of this contention, the

Office Action cites and attaches references that are mainly directed to antisense technology.

10. In response, attached hereto is Exhibit C, which provides data that show that ribozyme therapy is, in fact, much more "predictable" than antisense therapy. Specifically, Exhibit C shows the activity of 6 ribozymes which were designed according to the applicable rules for hairpin ribozymes to target six of the 12 possible ribozyme cleavage sites for IL-1 beta mRNA. All six ribozymes reduced mRNA levels greater than 50% and 5 out of 6 reduced protein levels greater than 50%.

I declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willfully false statements are punishable by fine or imprisonment under 18 U.S.C. Section 1001 and that any such statement may jeopardize the validity of the subject application or any patent issued thereon.

Joan Robbins

03/7/03
Date

EXHIBIT A

Experimental Design

Groups	Dose Mg left eye	Formulations	Treatment frequency	Number of animals	
				Males	Females
1 control	0	Solution	4 injections (D1, 4,8, and 11)	2	2
2	0.5	Solution	4 injections (D1, 4,8, and 11)	2	2
3	5	Solution	4 injections (D1, 4,8, and 11)	2	2
4 control	0	Gel 2	1 injection on Day 1	2	2
5	0.5	Gel 1	1 injection on Day 1	2	2
6	5	Gel 1	1 injection on Day 1	2	2
7	0.5	Gel 2	1 injection on Day 1	2	2
8	5	Gel 2	1 injection on Day 1	2	2

The dose volume was 0.05ml/Left eye/Animal.

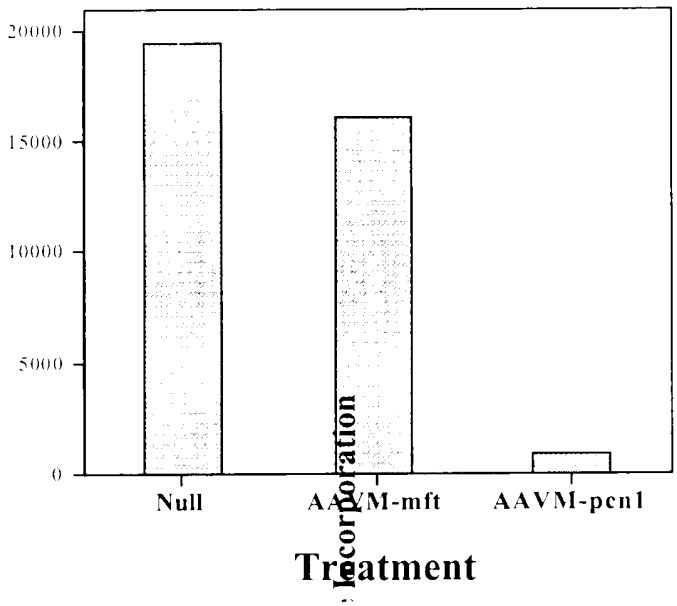
Results: Clinical Status of the trabeculectomy

Follow up days	Status of the trabeculectomy
Day 8	30/32 trabeculectomies are functional: 1 male in placebo Group and one male in Group 8
Day 14	20/32 trabeculectomies are functional: 18 were treated with PCNA synthetic ribozymes and 2 were controls

Results: Histopathologic evaluation

Animal Groups	Formulation	Histopathological findings	
		Open channels penetrating the sclera	Thinning of the sclera at the trabeculectomy site
1 Control	Solution placebo	1/4	1/4
2	PCNA solution - 0.5mg	1/4	2/4
3	PCNA solution - 5 mg	1/4	2/4
4 Control	Control Gel	1/4	3/4
5 - 6	Gel 1	3/8	6/8
7 - 8	Gel 2	2/8	3/8

EXHIBIT B



Null is a no treatment control.

AAVM-mft expresses an HIV ribozyme as a control.

AAVM-pcn1 expresses PCNA targeted ribozyme.

EXHIBIT C